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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,600	03/11/1999	YAROM COHEN	TPP30566	7243

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1653	19

DATE MAILED: 05/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/254,600	Applicant(s) COHEN, YAROM	
	Examin r Anish Gupta	Art Unit 1653	

-- The MAILING DATE of this communication appears on th cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-116* is/are pending in the application.

4a) Of the above claim(s) *63-65,67-92,94-109 and 113-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-62,66,93,110-112 and 116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] in Paper No. 17 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Although the Applicants did not specifically as such, the elected species reads on claims 59-62, 66, 93, 110-112 and 116. Accordingly, Claims 63-65, 67-92, 94-109 and 113-115 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 17.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 59-62, 66, 93, 110-112 and 116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For the analogs, the claims state "(as herein defined)." However it is unclear where the definition is found. The claim itself does not define the word analog. If applicants intent is that the definition is found in the specification that is improper since it is improper to incorporate limitation needed in the claims from the specification. Therefore the claims are indefinite. Further, it is unclear what modification would qualify a compound as an analog of any of the claimed comopunds.

In claim 59, it is unclear what is the intended meaning of "risk f actors" in line 2. It is believed that this is a typographical error.

Claim 59 utilizes improper markush language. The claim should say "selected from the group consisting of" instead of "selected among".

In claim 60, the word "Compound" should not be capitalized.

In claim 66, it is unclear as to the intent of bracketing and underlining. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. In the reply filed , applicant has used both underlining and bracketing in such a manner that it is unclear to the examiner whether the underlined and bracketed is intended to appear in the patent. The underlining and bracketing is unclear because all of SEQ. ID. identification numbers are both underlined, meaning addition to the claim, and bracketed, meaning deletion from the claim. Thus it is unclear if this is to be added or deleted from the claim. If underlining and/or bracketing is intended to appear in the claims in the published patent, such intention must be clearly indicated in applicant's reply to this notice.

In claim 66, it is unclear as to the intended meaning of Bzl=(a), Ahep=(b), Ahex=(c), Aoct=(d) recited in the claim.

In claim 66, in the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe a "]" is missing from the end of the peptide.

In claim 66, in the peptide Cyclo [Pro-phe-D-trp-Lys-Thr(Bzl)], a "[" should be used instead of "(" in the begining of the peptide.

Claim 111, states that the effective dosage of is calculated based on octreotide. It is unclear from the claim if the dosage claimed is limited to only octreotide or other somatostatin analogs. If the dosage is inclusive of other analogs, it is unclear how the calculation based on octreotide affect the dosage regiment for other analogs.

In claim 111 and 112, it is unclear if the dosage is in grams, moles, liters. The claims only state "μ/kg/day". The claims do no recite what concentration unit the dosage is in.

In claims 59 and 110 it is unclear what consitutes as a "cyclothiazideor". It is believed that it should be "cyclothiazide or". If this is correct, then, Applicants are requested to make the appropriate corrections.

In claim 110, it is beleived that "analgosand" should be "analogs and". Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 59-62, 66, 93 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Higuchi et al.

The claims are drawn to pharmaceutical formulation comprising the somatostatin peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe].

The reference teaches a pharmaceutical formulation comprising cyclo Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe], sodium 5-methoxysalicylate, microcrystalline cellulose, lactose and magnesium stearate (see col. 4, lines 34-40). The additional agents of sodium 5-methoxysalicylate, microcrystalline cellulose, lactose and magnesium stearate in the composition correspond to the "additional compound" limitation of claim 60-62 in the instant application. Therefore, the claims are anticipated by the reference

6. Claims 59-62, 66, 93, 110-112 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Veber et al.

Veber et al. teach that the cyclic peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] is 50 to 100 times more potent than somatostatin for the inhibition of insulin, glucagon, and growth hormone release (see abstract). The reference states that the cyclic somatostatin analog enhances the ability of insulin to control blood glucose when administered to diabetic animals (see page 1377). Finally, the cyclic analog has a slow metabolism and thus has a longer half life in vivo (see page 1377). Therefore it would have been obvious to use the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] instead of native somatostatin to treat insulin resistance because this somatostatin analogue has been shown to be 50 to 100 time more potent than somatostatin and since this somatostatin analog has a longer half life. Note that the specification states that one of symptoms of Syndrome X is high concentration of blood insulin as a result of increased secretion of insulin (see page 2). Since the reference teaches that somatostatin peptide suppressed insulin secretion, the reference teaches the treatment of a symptom of Syndrome X. The reference also teaches that the

somatostatin analog was given in the dosage of 50μg (see page 1376), thereby meeting the limitation of claim 111 and 112.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 59-62, 66, 93, 110-112 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orskov et al. in view of Veber et al.

The claims are drawn to a method of treating insulin resistance and treating Syndrome X in a patient by the administration of a somatostatin or a somatostatin agonist.

Orskov et al. teach the somatostatin analog octreotide improved insulin stimulated glucose disposal and increased the suppressive effect of insulin on the liver, indicated improvement of insulin sensitivity (see page 215). GH has been shown to decrease insulin sensitivity both in the liver and in peripheral tissues and the suppression of GH levels is probably at lease partly responsible of the improved insulin sensitivity following octreotide (see page 215). In previous studies using Octreotide, it had been demonstrated that glucose metabolism and insulin sensitivity had both been improved using a higher dosage of the analog (see page 215). The reference concludes the octreotide infusion

decreased insulin requirement and increased insulin sensitivity in IDDM patients (see page 215). The specification define insulin resistance in a patient as a decrease in the biological action of insulin in vivo and assessed b the rate of disposal of glucose from the bloodstream. Therefore, since the reference teach that glucose metabolism and insulin sensitivity was in improved in patients having Diabetes, insulin resistance would necessarily had to have been treated. The difference between the prior art and the application is that the reference does not specifically the specific somatostatin analog claimed, Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe], and does not teach the treatment of syndrome X.

Veber et al., however, teaches that the cyclic peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] is 50 to 100 times more potent than samtostatin for the inhibition of insulin, glucagon, and growth hormone release (see abstract). The reference states that the cyclic somatostatin analog enhances the ability of insulin to control blood glucose when administered to diabetic animals (see page 1377). Finally, the cyclic analog has a slow metabolism and thus has a longer half life in vivo (see page 1377). The reference also teaches that the somatostatin analog was given in the dosage of 50μg (see page 1376). Therefore it would have been obvious to use the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] instead of native somatostatin to treat insulin resistance because this somatostatin analogue has been shown to be 50 to 100 time more potent than somatostatin and since this somatostatin analog has a longer half life.

As for the treatment of Syndrome X, the specification states that Syndrome X is metabolic disease characterized by insulin resistance. Therefore, since insulin resistance is treated in a patient by somatostatin, Syndrome X would necessarily have to be treated in the same patient by a somatostatin or another analogue of somatostatin.

8. Claims 59-62, 66, 93, 110-116 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kollind et al. in view of Veber et al.

The claims are drawn to a method of treating insulin resistance and treating Syndrome X in a patient by the administration of a somatostatin or a somatostatin agonist.

Kollind et al. teach that posthypoglycemic insulin resistance can be reduced by the administration of somatostatin (see page 176). The reference concludes that somatostatin reduced insulin resistance following hypoglycemia in patients with IDDM (see abstract). After the administration of somatostatin, lower blood glucose levels were observed, indicating enhanced insulin sensitivity (see page 177). The difference between the prior art and the instant application is that the reference does not specifically the specific somatostatin analog claimed, H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH, and does not teach the treatment of syndrome X.

Veber et al., however, teaches that the cyclic peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] is 50 to 100 times more potent than samtostatin for the inhibition of insulin, glucagon, and growth hormone release (see abstract). The reference states that the cyclic somatostatin analog enhances the ability of insulin to control blood glucose when administered to diabetic animals (see page 1377). Finally, the cyclic analog has a slow metabolism and thus has a longer half life in vivo (see page 1377). The reference also teaches that the somatostatin analog was given in the dosage of 50μg (see page 1376). Therefore it would have been obvious to use the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] instead of native somatostatin to treat insulin resistance because this somatostatin analogue has been shown to be 50 to 100 time more potent than somatostatin and since this somatostatin analog has a longer half life.

As for the treatment of Syndrome X, the specification states that Syndrome X is metabolic disease characterized by insulin resistance. Therefore, since insulin resistance is treated in a patient by somatostatin, Syndrome X would necessarily have to be treated in the same patient by a somatostatin or another analogue of somatostatin.

9. Claims 59-62, 66, 93, 110-112 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. or Fueessl et al. in view of Veber et al.

The claims are drawn to a method of treating insulin resistance and treating Syndrome X in a patient by the administration of a somatostatin or a somatostatin agonist.

The references teach the administration of somatostatin analog SMS 201-995 to type-2 diabetic subjects. Fueessl et al. teach the improvement of glucose tolerance in obese individuals (see abstract). The reference of Williams

et al. teach that after suppression of SMS 201-995 to type 2 diabetic subjects, a suppression of plasma concentration of insulin were observed without deterioration in glucose tolerance (see abstract). Glucose tolerance was not significantly impaired and there was no significant difference either in mean plasma glucose concentration or in the area under the postprandial glycemic curve (see page 80). The instant specification states that results indicating suppression of insulin secretion without an impairment in glucose response, produced an improvement in insulin sensitivity (see page 23). Also, it should be noted that the specification states that one of the risk factors of syndrome X is increase of insulin in the blood. Thus suppression of insulin would be a treatment of Syndrome X risk factors. Also, since the references insulin sensitivity was in improved in patients having Diabetes, insulin resistance would necessarily had to have been treated. The difference between the prior art and the instant application is that the reference does not specifically the specific somatostatin analog claimed, H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH, and does not teach the treatment of syndrome X.. The difference between the prior art and the instant application is that the references do not teach the somatostatin agonist claimed.

Veber et al., however, teaches that the cyclic peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] is 50 to 100 times more potent than samtostatin for the inhibition of insulin, glucagon, and growth hormone release (see abstract). The reference states that the cyclic somatostatin analog enhances the ability of insulin to control blood glucose when administered to diabetic animals (see page 1377). Finally, the cyclic analog has a slow metabolism and thus has a longer half life in vivo (see page 1377). The reference also teaches that the somatostatin analog was given in the dosage of 50μg (see page 1376). Therefore it would have been obvious to use the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] instead of native somatostatin to treat insulin resistance because this somatostatin analogue has been shown to be 50 to 100 time more potent than somatostatin and since this somatostatin analog has a longer half life.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Christopher Low, can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

3/21/02

Anish Gupta

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